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The Nutritional Aspects of Certain Endocrine Disturbances: Numerous observations published during the past several decades have indicated a relationship between alterations of the nutritional state and endocrine disturbances, but these observations were either neglected or misinterpreted, and did not attain the significance they deserved. With recent developments in the knowledge of nutrition and refinements in materials and technics, it has become possible to correlate a group of endocrine syndromes with impairment of hepatic function on a nutritional basis.

Soon after the isolation of the first crystalline estrogen, it became apparent that this and related steroids are rapidly inactivated in the body.

The literature on the earlier studies has been reviewed elsewhere.

In an effort to elucidate the metabolism of the sex-endocrine steroids, the senior author, some eight years ago, devised an efficient technic for studying the problem in the intact animal. When a pellet of estrone, estradiol or estradiol benzoate was placed in the spleen of a castrate rat, so that the absorbed steroid first had to pass through the liver before reaching the systemic circulation, no estrogenic effect was demonstrable; nor was there an androgenic effect when pellets of testosterone, testosterone propionate or methyl testosterone were placed in the spleen. The livers of both male and female rats inactivated both estrogens and androgens. Transplantation of the spleen containing the pellet of steroid, and ligation of the pedicle after establishment of a collateral circulation, produced the specific estrogenic or androgenic effect according to the nature of the implanted pellet. There have been many other reports since these on the ability of the liver to destroy estrogens and androgens and there is now little doubt that inactivation of the sex hormones takes place in the liver.

During the period that these observations were being made, there were many reports concerning the production of hepatic lesions by nutritional deficiency. The method of splenic implantation of pellets of steroids immediately lent itself as a method of observing the effects of certain aspects of nutrition in relation to hepatic function. The authors found that castrate female rats with pellets of estrone in their spleens remained anestrus when on a normal diet, but went into continuous estrus when the diet was depleted of the B-complex vitamins. The addition of brewers yeast, or a mixture of crystalline thiamine, riboflavin, pyridoxine, and calcium pantothenate to the diet restored the anestrus state. Subsequent depletion of the vitamins again led to continuous estrus. The inactivating mechanism in the liver bears no necessary relation to detectable morphologic changes, since impairment of the mechanism took place in livers that appeared normal histologically, but inactivation can occur in livers that show necrosis and fat infiltration.

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Subsequent investigation of estrogenic inactivation by the liver indicates that in the type of experiments carried out, in the rat, thiamine and riboflavin alone, among the B vitamins, are adequate to permit hepatic destruction of estrogen. The presence of methionine appears essential to this function.

These studies were continued by analyzing the effect of these nutritional changes on the metabolism of androgen in the liver. The technics employed were similar. In contrast to the effect observed with the estrogens, there was no significant impairment of the ability of the liver to destroy androgen in deficiency of vitamin B complex. This observation indicated an alteration of the estrogen-androgen equilibrium and suggested a series of clinical studies on the relation of nutritional deficiency to syndromes in which this balance is disturbed. This soon led to the development of a rational method of therapy.

The fundamental work of R. T. Frank and his collaborators showed that certain forms of pathologic uterine bleeding, of premenstrual tension, and of chronic cystic mastitis were related to an excess of estrogen. Originally, these were thought to be caused by an excessive secretion of estrogen by the ovaries. However, in view of observations that the liver loses its power to destroy estrogen in deficiency of vitamin B complex, the relation of these syndromes to nutritional deficiency was investigated.

Liver poisons and cirrhosis of the liver have long been known to produce menorrhagia and metrorrhagia. The work of György and Goldblatt, and others has shown that cirrhosis of the liver can result from nutritional deficiency. The liver is protected against a variety of poisons by vitamin B complex. Goldberger reported that menorrhagia may occur in pellagra. In male patients with cirrhosis of the liver, urinary estrogen is increased and appears in the free form, but urinary androgen is reduced and is present only in combined form; these patients had gynecomastia, testicular atrophy, or both. Changes related to excess estrogen occur in the prostate glands and in the testes of patients with cirrhosis of the liver. A study of necropsy data on female patients who died of cirrhosis of the liver invariably revealed lesions in the pelvic organs identical with those induced by estrogenic stimulation. Even aged female patients dying of hepatic cirrhosis have a hyperplastic endometrium in the proliferative phase (G. R. Biskind, unpublished). The cutaneous spider-like vascular configurations and palmar erythema, formerly associated mainly with cirrhosis of the liver, have been shown by Bean to be related to nutritional deficiency and to the presence of estrogen in increased amounts. Administration of estrogen to patients with these cutaneous phenomena produced new lesions and exacerbation of those already present;

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regression followed withdrawal of estrogen. These observations are correlated with those of Reynolds and Foster who showed that estrogen causes dilatation of the minute vessels in the ears of castrated rabbits; and Bean has shown that the cutaneous vascular spiders are histologically similar to the spiral arteries of the endometrium observed by Bartelmez and by Jones and Brewer. Palmar erythema has been noted by Perera in nutritional deficiency and the regression of this lesion has been described in two cases of cirrhosis under dietary therapy. There have been many observations on the relation of estrogen to the menstrual cycle and to liver function, and these indicate that with increase in amount of body estrogen, either cyclically during the intermenstruum or in the latter part of pregnancy, there may be a concomitant drop in liver function. Delayed postpartum involution of the uterus and its complication of subsequent menometrorrhagia, cystic mastitis and premenstrual tension occurs as a result of impairment of hepatic function with the associated increase in body estrogen.

To summarize the experimental evidence: it is obvious from experimental observations in vitro and in vivo that the liver is the site of metabolic conversion of estrogens and androgens from physiologically active materials to inactive substances. The inactivation of estrogens in the liver is controlled by factors which influence the function of the liver, such as nutrition, poisons, and cirrhosis. Since metabolism of the androgens is not significantly affected by these factors, it becomes evident that serious alterations of the estrogen-androgen equilibrium in the body can occur on the basis of disturbances that impair hepatic function. With impairment of the estrogen-inactivating mechanism of the liver, there is a retention of body estrogen. The clinical evidences of excess estrogen in the female are menometrorrhagia, premenstrual tension, cyclic, painful enlargement of the breasts, chronic cystic mastitis, and if the condition is protracted, uterine myomas and other benign overgrowths, or malignant neoplasms of such tissues as uterus and breast, which are responsive to estrogen. The changes in the male are not quite so readily evident, but are equally frequent; these are testicular softening and atrophy, diminished libido and impotence, and infertility. Gynecomastia is also occasionally seen as a consequence of excess estrogen resulting from nutritional impairment of hepatic function. This lesion has recently been reported to have been quite common among our troops in the Pacific, who had been captured by the enemy and maintained for long periods on severely restricted diets. On the basis of the observations already described, the lesion was correctly related to the nutritional defect and it responded to dietary therapy.

Thus, the basic etiologic factors in certain pathologic entities become clarified: the constant stimulus of a high estrogen level in the body produces an endometrium that remains in a proliferative state throughout the cycle,

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then slowly progresses into a permanent hyperplastic state with irregular bleeding. The same stimulus applied over a period of years to the myometrium can induce localized or irregular hypertrophies and hyperplasias of the muscle with ultimate isolation of a nodule and the formation of a leiomyoma. It is well known that these tumors are related to the estrogen level of the body; regression after the menopause is almost invariable. In the same manner, it is possible to understand the development of chronic cystic mastitis; the continuous and additional cyclic stimulation of the breasts over a period of many years can ultimately lead to localized hyperplasia of glands and ducts; this is associated with irregular scarring or increase of fibrous tissue. That these hyperplastic lesions in the endometrium, cervix, and in the breast can ultimately become malignant is readily understandable, and the recent study by Ayre and Bauld on the relation of thiamine deficiency, high estrogen, and uterine cancer is a logical step which followed the earlier observations of the authors.

On the basis of experimental evidence that nutritional factors can control the metabolism of estrogen in the liver, patients exhibiting signs and symptoms of excess estrogen were studied. In every instance, it was possible to find evidence of nutritional deficiency in these patients; glossitis, cheilosis, and other signs of deficiency were observed and photographic records in color were made routinely before and after treatment with nutritional factors. Large doses of synthetic B-complex vitamins were administered, together with adequate amounts of a crude natural source of accessory vitamin B factors, preferably as whole desiccated liver or the fractions of liver containing the highest concentration of the nutritional factors. In more recent studies in man, the total daily dosage by mouth was given in divided doses after meals and consisted of from 38 to 45 mg. of thiamine, from 20 to 35 mg. of riboflavin, from 12 to 25 mg. calcium pantothenate, from 3 to 8 mg. pyridoxine, from 200 to 300 mg. niacinamide, 200 mg. choline, from 90 to 150 mg. inositol, and from 180 to 300 micrograms of folic acid derived, in part, from crystalline material and, in part, from natural sources. Desiccated whole liver derived from 45 to 75 Gm. of fresh liver, or liver fractions derived from 60 to 100 Gm. of liver, or combinations of the two were administered. In some cases, it was necessary to supplement this with frequent intensive parenteral administration of synthetic B vitamins, since preparations of liver extract for parenteral use are refined mainly for their antianemia potency and thus lose much of their effectiveness for nutritional therapy.

The results of this therapeutic program can now be evaluated on the basis of the authors' observation of three groups of patients, totalling more than 700, in widely separated communities, for periods up to five years, and on an additional large group reported to the authors in personal communications from physicians employing this program. The functional condition of

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the patients who were studied varied from simple premenstrual tension with slight menorrhagia and mastalgia to severe irregular metrorrhagia caused by cystic hyperplasia of the endometrium which is often associated with leiomyomata, or severe cystic mastitis of the breast. The response to intensive, persistent, and complete nutritional therapy was invariably excellent in all the syndromes related to excess estrogen. After the endocrine disturbance had been controlled and the nutritional lesions healed, it was nearly always possible to reduce the intake of B complex, although this usually had to be continued indefinitely thereafter in from five to ten times the maintenance amounts for normal persons. It is suggested that once tissues are depleted of these factors, changes may occur which require a greater amount of the vitamin than that needed for normal maintenance. Bessey and Lowry found that the level of riboflavin in the rat cornea reflects the riboflavin intake, but that once the animal has been depleted of riboflavin, administration of riboflavin fails to increase the content of the cornea to the original level. This appears to apply to the human being also, for higher levels must be maintained in depleted than in nondepleted individuals. It cannot be too strongly emphasized that adequate amounts of a satisfactory natural source of the nutritional factors must be included in the therapeutic regime. Failures will occur if only synthetic vitamin preparations are used, or if the amount of naturally-occurring material is insignificant, as in several commercial preparations which contain only a few grains of brewers yeast. In the management of premenstrual tension and mastalgia, if therapy is begun at the time of menstruation, definite changes will usually be noted at the next menstrual period and almost complete alleviation of symptoms will frequently be evident at the second period. With grossly irregular metrorrhagia, especially in individuals in whom the condition has existed for years, several months may be required to bring about regular cycles in which there is evidence of a secretory phase indicating ovulation. So-called "lumpy breasts" require a similar period of intensive treatment with equally satisfactory results; in a few instances, there has been a rapid retrogression of most of the irregular indurated masses, but one or two nodules have persisted. These were removed surgically and were found to be made up of scar tissue, nests of glands, dilated ducts, and small cysts.

On the basis of the experimental observations described, which in their broadest sense lead to the conclusion that there may be an impairment of hepatic function in certain nutritional deficiencies, investigation of other conditions related to impaired liver function was also undertaken. Experiments by Soskin et al. have shown that in the maintenance of normal carbohydrate metabolism, the liver plays a basic role, and that the liver is the site of the refractory state in insulin resistance. In pancreatectomized dogs, the diabetic state was exacerbated and the insulin requirements increased when the basic diet was devoid of B vitamins; the addition of yeast or of

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synthetic B vitamins reduced the insulin requirement to its former level. Biskind and Schreier indicate that the liver may be so altered by nutritional deficiency that it can no longer respond to endogenous insulin, thus inducing a failure in normal carbohydrate metabolism. The occurrence of lesions of the tongue in diabetes, now known to be characteristic of pellagra, was mentioned years ago by Stockton, and changes in the central nervous system in these cases, now known to be characteristic of thiamine and niacinamide deficiency, were mentioned by Fletcher. Thiamine, riboflavin, niacinamide, pantothenic acid, choline, ascorbic acid, and Vitamins A and D are all known to be involved in carbohydrate metabolism. The application of all these facts by M. S. Biskind and Schreier led to the treatment of diabetes on a nutritional basis. They observed an invariable association of avitaminotic lesions with the diabetic state. Partial or complete restoration of carbohydrate balance occurred in 94 patients receiving intensive and persistent nutritional therapy and the associated avitaminotic lesions cleared up at the same time together with alleviation of associated syndromes related to excess estrogen. In 25 patients, striking reductions in blood sugar level occurred on nutritional therapy alone; the insulin requirement was reduced in 14 persons, eliminated in 16 instances, and in 37 patients in whom it was left unchanged, the improvement in general health and well-being was striking.

Another point that requires discussion is the question of widespread low grade vitamin deficiency in the population as a whole. The tendency towards a highly purified diet, with a limitation of meat and whole grains and without vitamin supplements, may account for the presence of a much greater degree of nutritional deficiency in the population than is generally considered possible. The fact that in the average young female, the presence of various degrees of premenstrual tension, abdominal puffiness and premenstrual breast changes are considered normal concomitants of menstruation, is an indication that widespread deficiency is prevalent. All these signs and symptoms respond quickly to adequate nutritional supplements.

Summary and Conclusions. It has been demonstrated in experimental animals that the liver is the site of inactivation of estrogens and androgens and there is abundant evidence that these steroids are similarly metabolized in the human liver. The ability of the liver to metabolize estrogen is controlled by certain factors, among which is the intake of vitamin B complex. Inactivation of androgen in the liver proceeds without significant impairment even during deficiency of vitamin B complex. Thus, it appears that the estrogen-androgen equilibrium in the body is maintained by a normally functioning liver, and that the equilibrium can be altered by nutritional deficiencies which impair the ability of the liver to destroy estrogen. In females, the estrogen thus retained produces premenstrual tension, retention of body water, mastalgia, menometrorrhagia, chronic cystic mastitis and uterine

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myomas; following pregnancy, there is impaired involution of the uterus. In males, this syndrome leads to testicular atrophy, diminution in libido and potency, infertility, and gynecomastia. All these functional conditions respond readily to intensive and complete nutritional therapy; the organic changes likewise respond, although more slowly, and often less completely. Nutritional deficiency, with the concomitant accumulation of excess estrogen and the consequent prolonged stimulation of tissues of the uterus and breast, may lead to the development of precancerous hyperplasias and ultimately, in certain cases, to definite cancer. At the present time, it has been demonstrated in a large series of patients that the clinical signs and symptoms related to excess estrogen can be controlled by a therapeutic program that employs an adequate dosage of all the known and unknown factors of the vitamin B complex. The significance of nutritional deficiency in diabetes and its consequent impairment of hepatic functions has been shown in relation to the aforementioned syndromes. (Am. J. Clin. Path., Dec. '46 - G. R. Biskind and M. S. Biskind)

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Treatment of Ulcerative Colitis with Thiouracil: Laurence Martin, working in Cambridge, England, makes a preliminary report in the 28 December 1946 issue of the Lancet on the treatment of ulcerative colitis with thiouracil and methyl-thiouracil. When given these compounds, 4 patients experienced a rapid cessation of symptoms, a disappearance of blood and mucus with a return to formed stools, and evidence of improvement in bowel pathology on sigmoidoscopic examination. The author used 0.6 Gm. daily for from 6 to 10 days; then reduced the amount to 0.4 Gm. and later to from 0.2 Gm. to 0.1 Gm. daily. After studying the four patients, Doctor Martin believes that he reduced the daily dosage of thiouracil too quickly.

The author did not lose sight of the fact that ulcerative colitis is a chronic disease characterized by spontaneous and unpredictable remissions, and notes that further long-term observations alone can show whether thiouracil treatment can alter the natural course of the disease. Sufferers from ulcerative colitis are also readily influenced by spectacular remedies and suggestion, but in these cases thiouracil was given without comment or display of undue interest.

The mode of action of thiouracil can be only a matter for speculation at present, but it is clear that it did not produce frank hypothyroidism in these cases and so render the bowel transit sluggish.

It may be significant that thiouracil and methyl-thiouracil are chemically similar to synthetic 5-methyluracil, thymine, (Bumed News Letter of 8 Nov 1946)

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which Spies et al. found effective in treating the macrocytic anemia and diarrhea of tropical sprue; in these studies the interesting observation was made that stools became semiformal and reduced to one daily as early as the fourth or fifth day of treatment.

NOTE: Should the observations in this preliminary report prove thoroughly sound, the use of the less toxic propylthiouracil (Bumed News Letter of 5 July 1946) would suggest itself for trial.

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Study of Folic Acid and Liver Extract in the Treatment of Pernicious

Anemia: Because the treatment of pernicious anemia with folic acid alone for relatively short periods of time has not produced fully satisfactory results hematologically and neurologically, a study was undertaken to determine (1) the effects on the blood and nervous system of prolonged treatment with folic acid alone, and (2) whether a combination of folic acid with suboptimal doses of liver extract would produce a complete hematological remission and protect against or produce improvement of any existing signs and/or symptoms of CNS involvement. Of the twelve patients included in this study, 1 had a macrocytic anemia which followed extensive resection of the small and large intestine and was included because he presented a sprue-like syndrome. This patient with the postoperative macrocytic anemia was treated with folic acid only. Of the other 11 patients, 1 was also treated with folic acid only; 5 were treated first with folic acid, which after a while was discontinued and then treated with liver extract; and 5 were treated with folic acid in conjunction with suboptimal doses (1/2 unit) of liver extract.

The following observations were made:

Folic acid in daily doses of from 15 to 50 mg. given orally, or 20 mg. intramuscularly, in patients with pernicious anemia, usually produced a submaximal reticulocytosis as compared with results that would be expected and are usually obtained from liver extract. In 3 patients the hemoglobin and red cells rose to a level of about 12.0 Gm. and 4.3 million respectively without further rise after 3 months of therapy. Folic acid in these doses failed to prevent the development or progression of neurological symptoms indicative of subacute combined sclerosis.

In 5 patients, folic acid in oral doses of 5 or 10 mg. given daily in conjunction with 1/2 unit of liver extract injected intramuscularly daily also, produced a reticulocytosis greater than that anticipated from adequate liver extract therapy alone.

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With combined liver extract and folic acid therapy there was evidence of improvement in the symptoms and signs of subacute cord involvement in 3 patients.

Folic acid, combined with 1/2 unit of liver extract, was found to produce a complete hematological remission.

Folic acid, alone or in combination with small doses of liver extract, produced an improvement in appetite and general well-being in patients with pernicious anemia.

The possible enhancing effect of liver extract when combined with folic acid cannot be due to the folic acid content of the former since 1 unit of liver extract contains only 0.38 micrograms of folic acid.

Folic acid administered to the patient with the post-surgery macrocytic anemia produced a complete remission in the blood picture and a marked improvement in other signs and symptoms. (Blood - J. Hematol., Jan. '47 - L. M. Meyer)

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New Concept of Competitive Inhibition of the Renal Tubular Excretion of Penicillin: It has been established that penicillin is excreted by way of the renal tubules in addition to glomerular filtration. Its over-all clearance at all plasma concentrations studied to date appears to be equivalent to renal plasma flow, as measured directly or by PAH (p-aminohippuric acid). When a normal relationship exists between glomerular filtration and renal plasma flow, the fraction of penicillin filtered at the glomeruli represents in man about 20 per cent of the total amount excreted per unit time. At customary blood levels, about 80 per cent of the penicillin excreted is eliminated by way of the renal tubules. Thus, the suppression of penicillin excretion by the tubules could be expected to effect a considerably higher plasma concentration for a longer period of time than normally would obtain following a given dose of penicillin.

This reversible inhibition of the excretion of penicillin by the tubular epithelium has been effected by the administration of diodrast or PAH. These compounds are excreted by the same tubular transport mechanism and as rapidly as penicillin. Hence, it is possible, by maintaining a high plasma concentration of either compound, to saturate functionally that mechanism and thus suppress the tubular elimination of penicillin on what loosely may be considered a "mass action" basis. This principle has been applied successfully in therapy, but the very great amount of PAH needed to produce this effect coupled with its required intravenous administration seriously limits its practical applicability. Because of this a new approach was sought

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which resulted in the concept involving the application of the compound described herein.

The purpose of this report is to present briefly the broad aspects of this concept without detailed qualification or substantiation of each point (the laboratory and clinical substantiation will be submitted in detail in a forthcoming series of publications).

Excretion by the renal tubules is a remarkably selective process. The transport mechanism for the excretion of penicillin, like other differentiating mechanisms for glucose and amino acid reabsorption, is dependent on the viability of the tubular epithelium. It seemed desirable to inhibit the transport mechanism for the excretion of penicillin in a manner that would be both selective and reversible and thus not abolish other transport systems or impair the vitality of the cell as a whole. If this could be accomplished, the over-all excretion rates for penicillin should be markedly lessened. Although there may be a number of seemingly discrete systems, the functional orientations of which are directionally opposite within the cell (excretion-absorption), the multiple components of a single transport mechanism need not be unique, either descriptively or functionally, to that system that gains singularity only through some definitive component or components. Since most metabolic processes are enzymatic, it seemed possible to inhibit selectively such a fundamental or definitive enzymatic component of an otherwise complex process and so halt the particular system involved in the excretion of penicillin.

The competitive inhibition of the enzymatic alteration of one substrate by another which has an affinity for, but is refractory to, the action of an enzyme or enzyme system occurs in vitro. Examples of such in vitro substrate competition are the inhibition by malonate of succinate oxidation by the succinoxidase system, and the inhibition by ephedrine of tyramine deamination by amine oxidase. Moreover, the affinity of the competitive substrates appears to be for the definitive enzyme, succinic dehydrogenase or amine oxidase, in each complex system. These are reversible inhibitions in which the integrity of the enzyme system has not been violated inalterably.

Thus, in terms of renal physiology, if it were possible to find a compound which would inhibit the excretion of an agent by the tubules on the basis of specific enzymatic substrate competition, it should have the following essential chemical and pharmacodynamic characteristics: (1) It should have an affinity for the particular enzyme system that characterizes the selectivity of the over-all tubular mechanism for penicillin excretion. (2) If it is sufficiently different to be refractory to the action of that system, its

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renal elimination should be limited essentially to glomerular filtration. (3) The inhibition of penicillin excretion should be maximal at relatively low plasma concentrations, as compared with the type of mass action effect induced by PAH. (4) At plasma concentrations sufficient to inhibit maximally the tubular excretion of penicillin it should not alter the function of other transport mechanisms either selectively or collectively. (5) If the agent acts by competitive inhibition of an enzymatic reaction, in accordance with this concept, the process should be reversible. (6) Such a compound should not necessarily influence either renal blood flow or glomerular filtration rate. However, it would vitiate the use of PAH for the measurement of renal plasma flow or normal PAHT_m, for PAH is excreted in a manner similar to that for penicillin. (7) The agent should not have a high order of systemic toxicity. (8) The compound need not necessarily influence any properties peculiar to penicillin, such as its bacteriostatic action, inactivation, etc. It would follow from (2) and (3) that the dosage of the compound would be quite practical. It was anticipated that these properties might be contained in a compound or compounds having the additional advantage of oral efficacy at reasonable dosage.

Of the compounds synthesized for this research by the organic chemistry department of the laboratories where the author works, 4'-carboxyphenylmethanesulfonanilide incorporates essentially the properties listed above.

In an experiment penicillin was infused at a rate and in an amount that would permit a falling penicillin plasma concentration if this compound for study were not effective. Duplicate control penicillin and creatinine clearances were obtained. The drug then was injected as a priming and maintenance dose, its distribution in the body allowed to reach equilibrium, and additional penicillin clearances obtained. It was observed that the tubular excretion of penicillin was completely suppressed, as indicated by the rising penicillin plasma concentration, decreased penicillin clearance, and increased filtration fraction.

In two experiments dogs were administered 100,000 units of penicillin by stomach tube every 4 hours for 16 hours, including the 4-hour period during which the control curves for penicillin plasma concentration were obtained. Immediately after the 4-hour control blood samples were taken, each dog was given 100,000 units of penicillin plus 60 mg. per kg. of the drug by stomach tube, another curve for plasma concentration of penicillin being obtained over the next 4-hour period. It was found that in the control phase the maximal penicillin plasma concentrations were 0.8 and 1.2 units per c.c., and at 2 hours the values were less than the lower limits of the Florey cup-plate assay, 0.24 units per c.c. Following administration of

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drug and penicillin the maximal penicillin plasma concentrations were 2.85 and 3.6 units per c.c. In one instance the peak occurred at 2 hours following oral administration. At 4 hours the plasma concentration was still somewhat above 0.5 units per c.c.

Summary. It has been found that the excretion of penicillin by a renal tubular transport mechanism could be physiologically inhibited reversibly. The basis for this effect is thought to be one of substrate competition between penicillin, which is excreted by the tubules, and 4'-carboxyphenylmethanesulfonanilide, which is essentially refractory to excretion by that transport mechanism. (Science, Jan. 24, '47 - K. H. Beyer)

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The Pathogenesis of Acute Appendicitis: Of the numerous theories attempting to explain the genesis of acute appendicitis, only two are today sufficiently attractive to elicit general support. Although each of these two theories plausibly explains a different set of observations concerning the disease, neither accounts for all facts. It is the purpose of this paper to reconcile the two theories and to correlate all of the known data, including that hitherto not explainable.

One of the theories of the pathogenesis of acute appendicitis, propounded principally by Wangenstein and his associates, centers about the importance of obstruction of the lumen of the appendix. This theory is based on the observed frequency of such obstructions, on the increased intraluminal pressures found in inflamed appendixes, and on the experimental production of appendicitis by obstruction. It fails to explain the occurrence of groups of cases, the association of these with climatic change, the geographic distribution of infection, and the distribution of infection according to age and sex.

The other theory is really a group of theories, which assumes the existence of a labile factor in the appendix that responds to a variety of external and internal stimuli and, in so doing, causes injury to the appendix which permits bacterial invasion by the flora normally present. The labile factor varies with different investigators, but the view of Ricker, which assumes that change in vascular tone is the basis for the attack of appendicitis, is the starting point for this group of theories. Vascular or muscle spasm, altered permeability of capillaries, changes in local acidity, and other such phenomena have been proposed as the basic alterations; but the assumption of a labile element, capable of rapid response to stimuli, is the common factor in all. This theory accounts for the association of appendicitis with distant infections and, by bringing in the influence of climatic and other environmental alterations on vascular tone and on the total organism, explains the geographic distribution and the concurrence of infections.

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The two theories can be reconciled and subsumed in one, if it be postulated that (1) the attack of acute appendicitis follows obstruction of the appendix, and (2) the most common cause of the obstruction is the lymphoid tissue of the appendix, a labile structure capable of rapid change under stimulation.

The human vermiform appendix has a characteristic postnatal development involving both its lymphoid tissue and its muscularis. The lymphoid tissue reaches its maximum development in the first decade of life. This tissue is better developed in the male than in the female. The muscularis does not develop fully until the second decade, and it is only at this time that the lumen becomes small. The relationship between the amount of lymphoid tissue and the size of the lumen represents the ability of the lymphoid structure to obstruct the lumen. This relationship correlates well with the characteristic age and sex distribution of acute appendicitis. The lymphoid tissue is capable of rapid response to internal stimuli and to environmental factors. This makes understandable the geographic distribution of acute appendicitis with the increase of its incidence in periods of climatic variability and the relationship of this disease to distant infections. Whatever the mechanism of its swelling, the lymphoid tissue causes appendicitis by obstructing the lumen of the appendix. Obstructions of the lumen of the appendix other than those due to swollen lymphoid tissue are adequate causes of acute appendicitis, but do not explain the greatest number of cases of this very common disease. (Am. J. Clin. Path., Dec. '46 - M. G. Bohrod)

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Atherosclerosis and Arteriosclerosis in Dogs Following Ingestion of Cholesterol and Thiouracil: Since Anitschkow demonstrated in 1913 that lesions similar to those of human atherosclerosis develop in the arteries of rabbits fed large amounts of cholesterol, numerous investigators have attempted to produce experimental atherosclerosis by feeding cholesterol to other animals. However, these efforts have succeeded only in chickens and guinea pigs. Attempts to produce atherosclerosis in dogs, cats, and monkeys by cholesterol feeding have failed. The cholesterol added to the normal diets of these animals has not caused hypercholesteremia comparable with that occurring in rabbits.

Many investigators have shown that the thyroid gland plays a part in the regulation of serum cholesterol levels. The results of unpublished experiments have demonstrated that after thyroidectomy the addition of cholesterol to the diet resulted in marked hypercholesteremia in dogs. However, partial or complete removal of the parathyroid glands during the thyroidectomy made it difficult to maintain the dogs in a state of good nutrition.

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In this investigation the thyroid activity of 4 dogs was modified by the administration of thiouracil and the effect on the serum cholesterol levels and on the development of arterial lesions was studied. Hypercholesteremia was produced in three of the dogs and maintained for long periods by feeding them cholesterol after the function of the thyroid gland had been modified. The experiment was divided into three periods: an initial control period of eight weeks, a thiouracil-feeding period of eight weeks, and a thiouracil-plus-cholesterol feeding period of from 48 to 56 weeks. Three dogs (368, 377, and 378) were maintained on this regimen, but the fourth (376) was maintained in the third period on thiouracil without the cholesterol supplement, and thus served as a control animal. A daily dose of from 0.5 to 1.2 Gm. of thiouracil without cholesterol produced increases of from 50 to 140 mg. per hundred cubic centimeters in the average serum cholesterol content of all the dogs. This increase is of the same magnitude as that which follows thyroidectomy. For the three dogs, the daily administration of 10 Gm. of cholesterol and 40 c.c. of cottonseed oil in addition to the thiouracil resulted in extreme hypercholesteremia, and the elevation of the cholesterol level above the base line reached a maximum of 770, 980, and 2,000 mg. per hundred cubic centimeters. Maintenance of the high level of serum cholesterol depended on both the cholesterol intake and the dose of thiouracil. Whenever the dogs ate poorly (thus reducing the cholesterol intake), the serum levels fell. The dose of thiouracil was increased at three different times during the experiment. In general, on these occasions further increases in the cholesteremia occurred in the cholesterol-fed dogs but did not occur in the control dog receiving only thiouracil.

Arterial lesions were produced in the three dogs receiving cholesterol. The distribution of the arterial lesions was different from that observed in rabbits and was strikingly similar to that found in human arteriosclerosis. In morphologic characteristics the lesions varied from atherosclerotic lesions similar to those seen in rabbits to lesions with fibrosis, hyalinization, and calcification similar to those seen in man.

It is possible that the thyroid involvement in these dogs influenced the development of the arterial lesions in some way not connected with the hypercholesteremia. However, since no arterial lesions were found in the control dog that had similar thyroid involvement without marked hypercholesteremia, the cholesterol level seems to be the decisive factor.

It is probable that the fundamental disease process is the same in dogs and rabbits and that the differences in the distribution and the morphologic character of the arterial lesions are due to some unidentified anatomic factor. The ability of the dog to metabolize considerable quantities of cholesterol increased the difficulty of maintaining a condition of hypercholesteremia but

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did not prevent the development of arterial lesions after the hypercholesteremia was established.

The changes seen in the thyroids of all the dogs resembled those described as resulting from thiouracil administration in other species.

Although it appears that arteriosclerosis of man is too protean a disease to have a single cause, the results reported here justify the belief that at least in the cases in which arteriosclerosis follows hypercholesteremia, the disease is similar to that produced experimentally in animals. It seems important, therefore, to continue studies of factors which may modify the lesions following hypercholesteremia in experimental animals. (Arch. Pathol., Oct. '46 - A. Steiner and F. E. Kendall)

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The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants: Multiple lesions of the central nervous system characterized by wide dissemination, predilection for the white matter, perivascular position, inflammation, proliferation of histiocytes, giant cell formation, and associated demyelination, have been produced in several laboratories by intramuscular injection into monkeys of emulsions and extracts of rabbit brain. The procedure, however, involved as many as from 30 to 100 injections, and intervals of from 3 to 13 months were required before symptoms appeared. On the hypothesis that the lesions might result from the interaction between the brain tissue of the host and antibrain antibody formed to the injected material, it was considered of interest to study the effect of adjuvants on this process. Administration of a variety of antigens as an emulsion with aquaphor, paraffin oil, and killed tubercle bacilli as described by Freund and McDermott has yielded an enhanced immune response with a number of other substances. It was found that the clinical and pathological picture of acute disseminated encephalomyelitis, similar to that previously reported

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could be induced in a relatively short period by three injections of an emulsion of normal rabbit brain containing these adjuvants. At about the same time Morgan independently reported similar findings resulting in monkeys from the injection of emulsions, with adjuvants, of normal monkey spinal cord.

The etiology of the demyelinating diseases is as yet obscure. The considerable number of possible causative factors advanced and stoutly advocated serves to emphasize this. Infection, toxemia by endo- or exotoxins, the circulation of lipolytic substances, venous obstruction, and immune reactions or allergic manifestations have been proposed on the basis of clinical and pathological investigations. The essential unity of the demyelinating diseases has been repeatedly suggested and an increasing body of clinical and pathological evidence would seem to lend this conception some support. Disseminated encephalomyelitis has been conceived of as an acute form of multiple sclerosis and the striking resemblance between the acute lesions in the latter and the coalescent lesions in the former has been pointed out. The occurrence of a postinfectious type of disseminated encephalomyelitis, and more particularly the development of a comparable pathological picture following the repeated injection of rabbit spinal cord in the Pasteur treatment for rabies, aroused the suspicion that immunological (allergic) factors might play a part in the production of demyelinating lesions.

In summarizing the report of their study, the authors make the following statements:

A picture resembling acute disseminated encephalomyelitis in the human being has been regularly and rapidly produced in rhesus monkeys by injection of emulsions of adult rabbit and monkey brain administered with adjuvants.

No lesions of the central nervous system resulted from injection of similar emulsions of fetal rabbit brain or adult rabbit lung.

The experimental findings are in accord with the hypothesis that antibody to the injected brain emulsion reacts with the tissues of the nervous system of the animal to produce the pathological changes. (J. Exper. Med., Jan. 1, '47 - E. A. Kabat et al.)

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Some Effects of Injected Cytochrome C in Myocardial and Cerebral

Anoxia in Man: Anoxia is a problem of widespread clinical interest and has been attacked from many points of view. The authors have been interested in

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the possibility of combating the effects of tissue anoxia by enhancing the tissue uptake of oxygen and in this connection have concerned themselves more particularly with succinic acid and cytochrome C. This report deals with some effects on the heart and brain of the parenteral administration of cytochrome C under conditions of anoxia.

The method used for preparing the cytochrome C was that of Keilin and Hartree. The material obtained by this method was reconcentrated by being put through the 50 per cent ammonium sulfate precipitation a second time. The material was then sterilized by passing it through a Seitz filter. The cytochrome C thus obtained seems to be nontoxic except that on two occasions it produced a transient urticaria when injected into patients, one of whom had a history of asthma and the other, hay fever. It was found that cytochrome C not only appears to be nontoxic but that it is relatively stable in the body when injected.

Cytochrome C apparently exists in organs in suboptimal amounts in that there seems to be relatively more cytochrome oxidase present in the organs than is required for activation by the cytochrome C present. Hence, an added supply of cytochrome C could be expected to be effective. The authors have demonstrated that it is possible in animals to increase significantly the organ content of cytochrome C. The increase in organ content which they could produce following intravenous or intramuscular injection was of a magnitude sufficient to produce an in vitro increase in tissue oxygen consumption of from 50 to 100 per cent. Hence, they had reason to believe that they might be able to increase the tissue uptake of oxygen in the organs of human beings by the parenteral injection of cytochrome C.

Under normal conditions there would appear to be no purpose in increasing the tissue uptake of oxygen. Under conditions of anoxia, however, such an effect would be highly desirable.

The authors carried out studies in human beings to determine the effects of injections of cytochrome C in (1) myocardial anoxia and (2) cerebral anoxia.

The findings suggest that cytochrome C might be beneficial in clinical conditions associated with myocardial anoxia such as angina pectoris and acute coronary occlusion. The observations on four patients with angina pectoris indicate that cytochrome C is only moderately effective in increasing the capacity for physical exertion. In the one patient in whom electrocardiographic tracings were obtained during exercise with and without the injection of cytochrome C, the changes in the S-T segment induced by exercise without injection of cytochrome C were not observed when cytochrome C had been

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previously injected. In addition to these observations, made in acute experiments, further observations are desirable in regard to the chronic effect of repeated injections of cytochrome C in angina pectoris. Studies which the authors have made in patients with intermittent claudication and Raynaud's disease indicate that the effects on muscle ischemia resulting from the continued daily administration of cytochrome C may be quite striking. This has been borne out in early observations on patients with angina pectoris as well.

In three patients with acute coronary occlusion and myocardial infarction, 70 mg. of cytochrome C given intravenously seemed to have no immediate effect either on the electrocardiogram or on the subjective distress. In these cases the failure of cytochrome C to exert a favorable effect may be explained by the fact that it could not reach the infarcted and anoxic tissue because of the vascular occlusion.

The influence of cytochrome C on cerebral anoxia was studied through the determination of its measurable effects on visual discrimination and code transliteration in induced cerebral anoxia.

Cytochrome C is activated by, among others, the succinic-succinic dehydrogenase system. It might, therefore, be theoretically desirable to supply, with the added cytochrome C in the tissues, an activator like succinic acid. Experiments which the authors have conducted with a combination of succinic acid and cytochrome C suggest that the cytochrome C effect can, in fact, be enhanced by being so combined with succinic acid.

The possible clinical uses for cytochrome C are as numerous and as varied as the clinical conditions in which anoxia is thought to play a role. In the field of pediatrics, asphyxia of the newborn immediately comes to mind. The possibility of using cytochrome C to enhance the tissue uptake of oxygen is particularly intriguing in conditions associated with cerebral anoxia in view of two facts, namely, (1) of all organs the brain is probably the most sensitive to oxygen lack, and (2) of all organs the brain has the least content of cytochrome C.

Summary. 1. The effects of anoxia on the electrocardiogram can be prevented by the injection of cytochrome C.

2. Subjects seem to tolerate anoxia more easily when they have been previously injected with cytochrome C.

3. The effects of anoxia in impairing visual discrimination can be overcome by the intravenous injection of cytochrome C.

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4. The effects of anoxia in slowing the cerebral functions required in code transliteration can be overcome by the injection of cytochrome C. (J. Pediat., Dec. '46 - S. Proger and D. Dekaneas)

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The Control of Rat Ectoparasites with DDT: Field studies were initiated to determine the degree of control effected against rat ectoparasites by treating rat-infested premises with 10 per cent DDT dust. Eleven premises chosen for study were trapped before treatment, 1 week following treatment, and at approximately monthly intervals thereafter. From rats trapped in untreated premises, only the oriental rat flea, X. cheopis, was found in sufficient numbers and uniformity of distribution to permit an analysis of normal seasonal populations.

The treatment was effected by blowing the 10-per cent DDT dust into burrows and enclosed harborages with a cyanogas foot-pump duster and by sifting a light layer of dust along rat runways with hand-shaker dusters.

Spectacular and consistent control of X. cheopis resulted in all 11 establishments, with the percentage of residual control dropping off for the 4 months following treatment at the rate of approximately 5 per cent per month from an initial 99.3 per cent.

A degree of control was achieved against rat mites and rat lice, but data were insufficient to justify the statement of a definite percentage. (Public Health Reps., Jan. 17, '47 - R. G. Ludwig and H. P. Nicholson)

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Observations on the Nighttime Resting and Biting Habits of Anopheline Mosquitoes in DDT-Treated and -Untreated Buildings: Laboratory cage tests and controlled experiments in houses have clearly demonstrated that residual-spray deposits of DDT are lethal to mosquitoes for considerable periods. Although these tests gave valuable information on the durability of DDT residual deposits, they did not give information on the mortality of malaria mosquitoes naturally entering treated dwellings in search of a blood meal. In order to secure a lethal dose of DDT from residual deposits, mosquitoes must actually touch the material and be exposed to it for a considerable period. This period has been shown to vary, depending on the temperature, age of treatment, density and distribution of the DDT crystals, and the resistance of the individual mosquitoes. Thus, the habits of the mosquitoes in question are of prime importance in determining the likelihood of their being exposed to DDT deposits

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for a sufficient time to produce death. If, after entering a treated house, mosquitoes spend all or most of their time flying around, or if they proceed directly to a host, feed, and leave immediately, it is obvious that they would not secure a lethal exposure to the DDT. Although it has been known for some time that Anopheles quadrimaculatus mosquitoes spend most of their daytime hours resting quietly in dark, damp, cool, quiet places, no detailed information has been noted on their hour-to-hour activities in buildings during the night or on the length of time they rested on walls or ceilings before or after feeding. It was to gain some idea of these activities that the studies reported upon were undertaken.

The authors summarize their study as follows:

Anopheles quadrimaculatus mosquitoes that enter buildings to feed rest on the walls or ceilings for considerable periods of time before as well as after feeding.

The observed nighttime resting periods of unengorged and engorged A. quadrimaculatus females in an untreated building were not significantly different from each other. The resting period varied greatly, ranging from a few minutes to over 11 hours.

In treated buildings the observed resting period was much shorter than that for untreated buildings, and the range was much less, varying from a few to 90 minutes. The average observed resting periods for unengorged and engorged A. quadrimaculatus females were not significantly different from each other, being 40 ± 3 minutes for the former and 33 ± 4 minutes for the latter.

After treatment, the percentage of engorged females resting on the walls increased from 14 to 31 per cent, perhaps indicating that many of the unengorged mosquitoes are irritated by the DDT and leave before they attempt to bite. Immediately after spraying, irritation is produced in such a short time that considerable protection against biting is afforded.

In the untreated building, the number of A. quadrimaculatus females increased throughout the night, reaching a maximum about an hour before daylight, whereas after treatment, the largest number was present just after the influx at dusk, and only a small number of mosquitoes was present at any time during the remainder of the night. (Pub. Health Reps., Jan. 17, '47 - C. M. Tarzwell and F. W. Fisk)

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The Comparative Residual Toxicity of DDT to Anopheles Quadrimaculatus When Applied on Different Surfaces: Subsequent to initiation of the extended malaria-control program by the United States Public Health Service, many types of households in various sections of the country were sprayed with DDT. In the treatment of buildings, surfaces were encountered which varied from those of household walls and furnishings to those of outbuildings and barns. The precautions against damage to surfaces varied considerably according to the surface treated. Since the success of the control program and the future practical field use of DDT in homes depended upon the satisfaction of the householder, knowledge concerning the residual effect of DDT treatments on different surfaces, the precautions necessary in application, and the amount of spray required for effective mosquito control was essential.

These investigations were initiated to determine the following factors: (1) the comparative residual toxicity of DDT sprayed on different materials; (2) the effects of spray applications on different surfaces; and (3) the effect of surface on the final residue distribution.

From the results of their study the authors summarize and conclude their report as follows:

It has been ascertained that the relationships between various types of household wall surfaces and the residual toxicity of DDT deposits are important factors in the practical use of DDT sprays.

The type of surface influences the residual toxicity of DDT sprays applied at equal rates. DDT on rough wood, fabrics, well-dried paints, and rubbing varnish gives the best residual effect. DDT spray applications on linoleum, fresh paints, spar varnish, or on simulated adobe are not effective against A. quadrimaculatus under test conditions. Under the conditions described, even applications of 600 mg. DDT per square foot are ineffective on adobe.

DDT sprays do not damage plastic screen or fabrics which are composed of plant or animal fibers. If applied too heavily, they cause some clouding of high-gloss enamels and some staining of wallpaper. DDT sprays, with either kerosene or Velsicol AR-50 as solvents, produce less deleterious effects on dark-gloss enamels than do the DDT-xylene emulsions.

The nature of the surface definitely affects the final distribution of the DDT deposits. Fabrics, wallpaper, and rough wood tend to hold the crystals on the surface, whereas plain, smooth wood is penetrated by the spray and a considerable portion of the spray deposit remains beneath the surface. Linoleum, fresh paints, and varnishes are readily penetrated by the solvents, and some of the DDT crystals are thereby permanently or temporarily occluded.

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The incorporation of salt into whitewash produces more effective DDT residual deposits on the outer surface of the whitewash. Grease or smoke depositions on surfaces previously treated with DDT decrease the efficiency of the residuals. (Pub. Health Reps., Jan. 31, '47 - J. M. Clapp et al.)

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Abstracts of Reports on Research Projects:

X-191
Rep. No. 5
14 Nov. '46

Use of Radioactive Hydrogen for Measurement in Vivo of Total Body Water.

With the advent of radioactive hydrogen of mass 3, tritium, it appeared practicable to utilize tritiated water for the measurement of total body water. The tritium was obtained by cyclotronic deuteron bombardment of beryllium and subsequent treatment of the beryllium target to form water. A method was developed for the determination of the activity of this water. This involved modification of the Geiger-Mueller counter tube so as to permit introduction into the tube of measured amounts of radioactive water vapor, alcohol, and argon. It was possible to evacuate and rinse the tube before each determination. Water of known activity was injected into two rabbits and one man and the plasma activity determined after a period of equilibration.

The body water of the human subject determined in this way agreed to within less than 1 per cent with the value calculated from specific gravity, assuming body water to constitute 73.2 per cent of the lean body mass. The values obtained for the two rabbits agreed to within less than 5 per cent with the water content determined by desiccation and weighing.

Less than 30 minutes was required for essentially complete distribution of the tritiated water in the body water of rabbits, and approximately one hour for the man. Consideration of these data and those of other investigators using deuterium oxide indicates a relationship between body size and rate of equilibration.

The tritium method at present appears to yield results with an accuracy as good as that obtained by the use of deuterium,

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and greater accuracy is expected with improvements in technic and the forthcoming availability of tritium of higher specific activity. (Nav. Med. Res. Inst., Bethesda, Md. - Pace et al.)

X-222
Rep. No. 8
4 Dec. '46

A Rapid Method for the Staining of Rickettsia Orientalis

It has been found that Giemsa's stain is not entirely satisfactory for the staining of R. orientalis grown in the yolk sac tissues of the hen's egg. Because of this, a screening process on approximately 30 dyes and stains was carried out from which it became apparent that methylene blue and its derivatives or combinations were the most useful stains for the identification of this organism.

Because MacNeal's tetrachrome blood stain (an economical and satisfactory imitation of Leishman's stain) contains methylene blue, a sample of it was obtained and tried. Its initial use proved sufficiently satisfactory for continued study. Repeated observations and modifications made it possible to devise a staining technic that is simple, rapid and reliable.

The staining procedure is carried out in Coplin jars. A stock solution of the tetrachrome stain is prepared according to the directions of the manufacturer. The working solution is unbuffered; the optimum pH is 6.5-7.0. The directions for staining are:

- a. Prepare smears from infected yolk sacs in the usual manner and allow to air dry.
- b. Fix and kill the preparations in absolute methyl alcohol for 3-5 minutes.
- c. Prepare the working solution of the stain by adding 4-5 ml. of the stock solution to 75 ml. of distilled water.
- d. Remove the slides from the fixative and place immediately into the stain with gentle agitation. Stain for 15-20 minutes.
- e. Clear the preparations by dipping into absolute acetone until the stain no longer dissolves from the smear.
- f. Blot dry and examine under the oil-immersion lens using a blue, ground-glass filter.

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Slides prepared in this manner show consistent and uniform staining. The color is retained without fading for at least 12 months. The background of the slide is a pinkish hue; the Rickettsia are stained a characteristic dull blue; erythrocytes and leucocytes are differentially stained. Bacterial contaminants are readily identified by their intense blue color and relatively large size.

It was found that the advantages of the tetrachrome technic for the staining of R. orientalis in yolk sac smears are:

- a. The stain is readily available either in powder or liquid form from commercial companies and remains stable over a long period of time.
- b. The fixing procedure reduces to a minimum the chance for accidental infection from the slides.
- c. The short staining time enables the laboratory to accommodate approximately three times as many slides daily as could be handled using Giemsa's stain.
- d. The simplicity and reliability of the procedure makes it possible for inexperienced personnel to obtain good results with the staining of yolk sac cultures of R. orientalis.

In the tetrachrome technic, the following disadvantages were observed:

- a. The stain is not so intense as Giemsa's and does not lend itself to morphological studies or photomicrographs.
- b. The technic does not produce consistent results in the staining of R. orientalis in animal tissues such as spleen and liver smears from mice and guinea pigs. (Nav. Med. Res. Inst., Bethesda, Md. - Diercks and Tibbs)

X-756
Rep. No. 1
13 Oct. '46

Observations on the Production of Hydrogen Sulfide by Shigella Alkalescens.

During the past three years, while attached to the Enteric Pathogen Laboratory of the Naval Medical School, National Naval Medical Center, the authors made observations on strains of Shigella alkalescens isolated from patients and asymptomatic subjects who were stationed in various geographic areas. It appeared worth while to assemble the

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results of the routine tests for H₂S that had been made on these cultures and to repeat the tests on those strains that had been preserved in stock.

One hundred and sixty-six cultures isolated from 141 individuals were listed; of these, 95 cultures from 89 individuals were available for reexamination. All strains conformed biochemically and serologically to the characteristics of S. alkalescens although tests were not made for antigens A, B, C, and D. The lead acetate paper method for detecting H₂S formation was used throughout and incubation was at 37° C. for a minimum of four days in instances of negative findings.

The observations made confirm the findings of Galton and Hess that some strains of S. alkalescens from large amounts of hydrogen sulfide. In this series of 166 cultures examined, over one-half were capable of this activity. The majority of changes noted upon repeat tests were from negative to positive since 31 strains fell into this category, but only two cultures exhibited a change from weak positive to negative. It appears justifiable to conclude that formation of H₂S by S. alkalescens conforms to the bacteriologic adage that a highly constant feature is variability. (Nav. Med. Res. Inst., Bethesda, Md. - Barnes and Casterline)

NOTE: Those interested in seeing copies of the complete reports should address their request to the Research Division, BuMed.

Opinions or conclusions contained in these reports are those of the authors. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department. Reference may be made to those reports marked "Not Restricted" in the same way as to published articles noting authors, title, source, date, project number, and report number. No part of the content of RESTRICTED reports may be published, reproduced, or referred to in articles for publication without permission obtained through the Bureau of Medicine and Surgery.

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Postgraduate Training in Allergy: The Bureau of Medicine and Surgery announces the opportunity for medical officers to obtain a twelve months' course in Allergy to be given at the University of Illinois College of Medicine, Chicago, Illinois, beginning 1 January 1948. This course of instruction will include work of the basic sciences underlying this specialty and will be supplemented by further clinical training. Requests are desired from medical officers of the regular Navy and should reach BuMed prior to 1 September 1947. (Professional Div., BuMed)

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Medical Library Requirements: Copies of pamphlet NavMed 1129 revised in December 1946 and entitled, Minimum Library Requirements for Hospitals of the United States Navy Approved for Internship Training and Residency-Type Training, have recently been forwarded to the hospitals concerned together with a letter from the Surgeon General. This pamphlet, a copy of which may be had from the Bureau upon request, contains the revised list of books and medical journals recommended by the Advisory Board and approved by the Surgeon General.

The addressees were directed to augment their libraries to include all books on this list. The Bureau arranges for furnishing the hospitals with the required medical journals.

The Surgeon General states that naval hospitals to be approved for internship training and residency-type training in specialties by the Council on Medical Education and Hospitals of the American Medical Association and by the American College of Surgeons must, in addition to other requirements, maintain libraries meeting minimum requirements. This is necessary in order to acquire and retain such official approval listing.

Libraries, particularly those in hospitals designated for the treatment of special types of diseases or injuries should cover needs at the discretion of the medical officer in command by additional books or by justifiable request to BuMed for special periodicals additional to those listed.

Lists of dental and nursing books are not included in NavMed 1129. It is directed that they be maintained as heretofore.

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Course in Aviation Medicine: See AlNav 26, page 33 of this issue.

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Attention Naval Reserve Officers:

Opportunity for Active Duty. The attention of Reserve medical officers and of pharmacists is invited to the opportunity to return to active duty at (1) one of the major naval air stations of the Naval Air Reserve Training Command or at (2) one of the Naval Air Reserve Training Units (NARTUs), each as listed below:

Major Naval Air Stations
of the Naval Air Reserve
Training Command

NAS, Atlanta, Ga.
NAS, Columbus, Ohio
NAS, Dallas, Texas
NAS, Glenview, Ill.
NAS, Grosse Ile, Mich.
NAS, Los Alamitos, Calif.
NAS, Memphis, Tenn.
NAS, Minneapolis, Minn.
NAS, New Orleans, La.
NAS, New York, N.Y.
NAS, Oakland, Calif.
NAS, Olathe, Kas.
NAS, Squantum, Mass.
NAS, St. Louis, Mo.
NAS, Willow Grove, Pa.
NAS, Denver, Colo.

Naval Air Reserve
Training Units
based at

NAS, Anacostia, D.C.
NAS, Jacksonville, Fla.
NAS, Miami, Fla.
NAS, Norfolk, Va.
NAS, San Diego, Calif.
NAS, Seattle, Wash.

Reserve medical officers and pharmacists who are interested in active duty at one of the stations or units listed above should initiate letters to the Bureau of Naval Personnel, via the Chief of Naval Air Reserve Training, Naval Air Station, Glenview, Ill., and BuMed, listing three or four stations at which duty is desired in order of preference. Personnel are desired in ranks not above that of commander in the Medical Corps.

Officers qualifying for the above billets are advised that, consistent with the needs of the Service, every effort will be made to continue them in their assignments. Certain of the above billets carry orders to duty involving flying for designated naval flight surgeons. Government quarters are available at many of the major naval air stations.

Organized and Volunteer Reserve Affiliation. Naval Reserve flight surgeons who desire to join one of the Naval or Marine combat air groups of the

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Organized Reserve training at one of the stations listed should contact the local commanding officer for additional information. (Personnel Div., BuMed)

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Reserve Medical Officers Needed for Combat Air Group Training Course:

Reserve Medical Officers will be needed for a two weeks' training course of Navy and Marine combat air groups of the Naval and Marine Air Reserve Training Commands. It is anticipated that the first of these periods will occur in the month of June, 1947. Interested officers below the rank of Captain are invited to communicate with the Staff Medical Officer of CNAResTra, NAS, Glenview, Ill., stating geographic area where duty is desired, and the date which will be most convenient to attend. (Personnel Div., BuMed)

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Naval Dental Motion-Picture Films Available to Civilian Dental Societies:

The attention of all dental officers is invited to the announcement, appearing on page 1597 of the December issue of the Journal of the American Dental Association, concerning motion-picture films that were produced by the Naval Dental Corps and now have been loaned to the American Dental Association for use by component societies.

Dental officers may advise civilian dentists who desire to borrow such films to request them from the Bureau of Public Relations, American Dental Association. (Dental Div., BuMed)

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Schedule of Sectional Meetings of American College of Surgeons for 1947:

The American College of Surgeons announces the schedule of their sectional meetings to be held during 1947:

<u>Date</u>	<u>City</u>	<u>Headquarters</u>
Monday-Tuesday March 10 - 11	Baltimore	Lord Baltimore Hotel
Friday-Saturday March 14 - 15	Atlanta	Atlanta-Biltmore Hotel
Thursday-Friday March 20 - 21	Fort Worth	Hotel Texas
Friday-Saturday March 28 - 29	Providence	Providence-Biltmore Hotel

(Not Restricted)

<u>Date</u>	<u>City</u>	<u>Headquarters</u>
Monday-Tuesday April 7 - 8	Omaha	Hotel Fontenelle
Monday-Tuesday April 21 - 22	Vancouver	Hotel Vancouver
Monday-Tuesday April 28 - 29	San Francisco	Fairmont Hotel

NOTE: Medical officers who desire to attend these sectional meetings may be given "authorization orders" upon request of BuMed.

(Professional Div., BuMed)

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Guest Lecturers and Clinicians at the U.S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland: As announced in the Bumed News Letter of 17 January 1946, the U.S. Naval Dental School sponsors the presentation of several outstanding lecturers and clinicians each month. All dental and medical officers of the Navy, regular or Reserve, whether on active duty or in an inactive status, dental and medical officers of the Army, regular or Reserve, and of all other federal services, and civilian dentists and physicians who are affiliated with accredited professional societies who reside in, or who are sojourning or visiting in the District of Columbia or its environs, are cordially invited to attend these meetings.

The following are the guest lecturers and their subjects which were scheduled for February and the first part of March 1947:

Feb. 7 - Harry Kaplan, D.D.S. - "The Treatment of Periodontoclasia." The lecture was illustrated by lantern slides and a colored moving picture of the surgical procedure. Doctor Kaplan is one of the pioneers in the treatment of periodontal diseases. He is an officer in the Dental Corps, U. S. Naval Reserve and practices in Washington, D. C.

Feb. 14 - Captain J. A. Walsh, DC, USN - "Organization of Dental Departments at Naval Training Stations." The dental organization of naval training stations was explained in detail,

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and the forms used, etc., in such organization were shown. Captain Walsh has had extensive experience in such organization.

Feb. 19 - Oscar V. Batson, M.D.; Malcolm W. Carr, D.D.S.; and James E. Aiguier, D.D.S. - "Acute Infections of the Maxillo-Facial Area and Other Surgical Conditions of the Mouth." Doctor Batson is Professor of Anatomy, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. Doctor Carr is Director of Oral Surgery and Visiting Oral Surgeon of the Metropolitan and Knickerbocker Hospitals. He is also Attending Oral Surgeon at St. Luke's Hospital and New York Polyclinic Medical School and Hospital, New York City. Doctor Aiguier is Assistant Professor of Oral Hygiene and Director of the courses of Oral Hygiene, School of Dentistry, University of Pennsylvania. He is Visiting Oral Surgeon, Presbyterian and Abbington Hospitals, Philadelphia, Pa.

This symposium is designed to correlate surgical anatomy, surgical pathology, operative surgery and materia medica and therapeutics in relation to surgical diseases of the mouth, with special reference to the acute infections of dental origin. The morning session will begin in Room 244 and will be conducted by Doctor Batson. The afternoon session will begin at 1300 in Room 244 and will be conducted by Doctor Carr and Doctor Aiguier.

Feb. 21 - Charles Baynes Hall, D.D.S. - "Bridge Abutments Preparation and Procedure." Doctor Hall practices in Washington, D.C., and has had extensive experience in this field. The lecture is supplemented by lantern slides and a moving picture. The lecture will be held in Conference Room 244 promptly at 1500.

Feb. 28 - W. T. Birthright, D.D.S. - "Porcelain and Acrylic Jacket Crowns." Doctor Birthright's moving picture on this important subject was only recently completed and has been shown only once, at the Greater New York Meeting. Doctor Birthright holds a commission in the Dental Corps, U. S. Naval Reserve and practices in Washington, D. C. The lecture will be held in Conference Room 244 promptly at 1500.

Mar. 7 - Carlisle C. Bastian, D.D.S. - "Porcelain Jacket Crowns." Doctor Bastian, who practices in New York City, is a pioneer in porcelain jacket crown restoration. He will discuss the technic for securing a lifelike appearance to porcelain

(Not Restricted)

jacket crowns, the preparation of teeth for porcelain jacket shoulder crowns, and also a shoulder-less preparation and the substitution of a gold shoulder for the shoulder on the tooth. A series of Kodachrome slides, presenting technic and cases before and after treatment will be shown. Conference Room 244 at 1300.

Mar. 14 - T. C. Schoonover, PhD. - "Status of Acrylic Resins." Doctor Schoonover, Chief of the Dental Materiel Section, National Bureau of Standards, Washington, D. C., will discuss some of the difficulties encountered in the processing of acrylic resin. Conference Room 244 at 1500.

NOTE: Because of unavoidable circumstances in completing arrangements for all of the lectures, it was not possible for the previous list, in the 17 January 1947 issue, and this one to be made available for an earlier issue of the Bumed News Letter.

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(Not Restricted)

Public Health Foreign Reports:

<u>Disease</u>	<u>Location</u>	<u>Date</u>	<u>No. of Cases</u>
Cholera	Afghanistan, Urgun District, China Khwa	Nov. 16-23, '46	30 (10 fatal)
Plague	Brazil, Minas Geraes State, Serro	December '46	12
Smallpox	China, Hong Kong	Dec. 7-21, '46	258
	Colombia	November '46	165 (4 fatal)
	Ecuador	November '46	28 (2 fatal)
Typhus Fever	Colombia	November '46	218 (8 fatal)
Yellow Fever (suspected)	French Equatorial Africa, Ubangi Shari Dept., Carnot	Dec. 14-21, '46	1 (fatal)

(Pub. Health Reps., Jan. 17 and 24, '47)

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ALNAV 26

24 January 1947

(Not Restricted)

Subj: Course in Aviation Medicine

Applications are desired to reach BuMed prior 15 March 1947 from medical officers regular and Reserve rank lieutenant (jg), lieutenant, lieutenant commander for three months course in aviation medicine at School of Aviation Medicine Pensacola Florida. Class convenes on 7 May 1947 quota twenty students. Aviation medicine training provides basis for later assignment in aviation medical research or other postgraduate training.

--SecNav. James Forrestal

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ALNAV 30

31 January 1947

(Not Restricted)

Subj: Re Use and Issue of Certain 1,000 c.c. Bottles of Saline

Discontinue use and issue until further notice sodium chloride isotonic solution 1,000 c.c., 6S, Stock Number 1-429-500 BuMed section Catalog of Navy Material, manufactured by Don Baxter Incorporated, Glendale California. All intravenous solutions should be inspected for particulate matter and discoloration prior to use. Units having such characteristics shall be surveyed together with all other units of the same lot number indicating lot number and manufacturer on the survey. All activities having suitable facilities shall determine the pH of representative sample of each lot of all types of intravenous solutions on hand and report manufacturer, lot number, and pH to Materiel Division, BuMed, Brooklyn, New York via air mail.

--SecNav. James Forrestal

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Circular Letter 47-6

22 January 1947

(Not Restricted)

To: All Shore Stations

Subj: Annual Estimates of Expenditures, FY 1948 under appropriation,
"Medical Care"

Ref: (a) BuMed ltr BuMed-Fa-HFM-hwl, L1-2/EN10(073), dtd 7 July 1945, (NavMed 855 Reprint of Navy Dept Bulletin 45-801, 15 July 1945.)

(Not Restricted)

This letter, together with seven (7) enclosures, from the Deputy and Assistant Chief of BuMed points out it is anticipated that the title of the appropriation "Medical Department, Navy" will be changed to "Medical Care," and directs (1) that the enclosures be used for preparing estimates under BuMed's appropriation, (2) that the estimates in duplicate will be furnished to reach BuMed on or before 1 March 1947, and (3) that any shore station that does not require funds under the cognizance of BuMed need not submit estimates.

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Circular Letter 47-7

22 January 1947

(Not Restricted)

To: MedOfsCom, NavHosps

Subj: Form NavMed-567, Register No. 1, Charge Register Sheet.

This letter from the Deputy and Assistant Chief of BuMed states that subject form is being revised for use beginning 1 July 1947 and that the present shortage of the old forms at supply activities can be overcome by addressees forwarding any excess above needs to BuMed for redistribution upon application.

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Circular Letter 47-8

27 January 1947

(Not Restricted)

To: Commanding Officers of Marine Corps Posts and Stations and Naval Hospitals within the United States.
All disbursing officers, Supply Department, within the United States.

Subj: Rental allowance, Marine Corps officers without dependents.

This is a joint letter from the Chief of BuMed and the Major General Commandant of the U.S. Marine Corps and states that on and after 1 January 1947 the instructions set forth in Art. 24-28 MCM will govern the payment of rental allowance to officers without dependents on duty within the United States.

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Circular Letter 47-9 28 January 1947 (Not Restricted)

To: MedOfsCom, NavHosps

Subj: Operation of Professional Libraries in Naval Hospitals.

This letter from the Chief of BuMed states that it is essential that MedOfsCom of NavHosps see that the professional libraries are adequate in size, free of noise, well lighted, suitably furnished, and readily accessible; and that the use of the library facilities should be made easy and attractive to those whom the library is designed to serve.

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Circular Letter 47-10 28 January 1947 (Not Restricted)

To: MedOfsCom, NavHosps (Cont.), plus Aiea, T. H.

Subj: Intern Training in Naval Hospitals

Ref: (a) NavMed-762 (Revised) dated 21 June 1946.

This letter from the Chief of BuMed directs that the addressees survey the training that each intern will receive during the 1946-47 intern year and insure that, in accordance with reference (a), no deficiencies exist. It is further pointed out that as the patient census drops and as the hospital personnel demobilization roll-up schedule proceeds it will be necessary to make some adjustments. The addressees are to report to BuMed that internships are not deficient in accordance with reference unless found to be otherwise, in which case the deficiencies discovered should be made known to BuMed together with recommendations for their correction.

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Circular Letter 47-11 30 January 1947 (Not Restricted)

To: All Ships and Stations

Subj: Transfer of Inactive Medical Department Records and Medical Department Records of Decommissioned Activities to Naval Records Management Centers.

This letter from the Chief of BuMed (see Navy Department Semimonthly Bulletin of 31 Jan 1947) modifies the instructions in certain previous directives on this subject.

Circular Letter 47-12

30 January 1947

(Not Restricted)

To: All Naval Stations and Hospital Ships

Subj: NavMed-I (Weekly Report of Patients), revised form.

Ref: (a) CirLtr No. 46-159 dtd 31 Oct 1946.

This letter from the Chief of BuMed directs that the addressees use only the latest form, NAVMED-I (Revised 11-45), in making the Weekly Report of Patients and that it be submitted in accordance with reference (a).

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